CASE REPORT

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Diagnostic Pitfalls of a Newborn with Congenital Nephrogenic Diabetes Insipidus

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What is already known on this topic?

Nephrogenic diabetes insipidus (NDI) is caused by antidiuretic hormone (ADH) resistance in the principal cells of the renal collecting ducts which results in impaired water reabsorption. NDI is a rare cause of hypernatremic dehydration in the neonatal period.

What this study adds?

Early partial but transient response to ADH is possible in NDI.

Abstract

Congenital nephrogenic diabetes insipidus (NDI) is a rare cause of hypernatremia in newborns. Central diabetes insipidus (CDI) is the main differential diagnosis in NDI, however NDI responds poorly to desmopressin acetate (DDAVP) treatment, while this is the mainstay of CDI management. Therefore, early and correct diagnosis of NDI is important to avoid the complications of inappropriate therapy. We report a newborn with hypernatremia and hypotonic polyuria. The patient was initially responsive but subsequently unresponsive to intranasal DDAVP treatment in terms of both urine output and serum sodium levels. A novel hemizygous missense mutation (c.632T > C, p.L211P) in the *AVPR2* gene was found in both the baby and his mother, and the diagnosis of congenital NDI was established. After hydrochlorothiazide treatment and hypo-osmolar formula were given, urine volume was decreased, and serum sodium levels were normalized. Early recognition and appropriate management of NDI may prevent complications of hypernatremic dehydration in young infants.

Keywords: Nephrogenic diabetes insipidus, neonate, hypernatremia, AVPR2

Introduction

Nephrogenic diabetes insipidus (NDI) is a disorder of water reabsorption, caused by the resistance in the principal cells of renal collecting ducts to antidiuretic hormone (ADH). Genetic forms of NDI are most commonly seen in early life and 90% of cases are caused by a mutation in the *AVP2R* gene that is located on the X chromosome (1). The other 10% is inherited autosomal recessively or dominantly due to a mutation in the gene encoding the aquaporin-2 water channel (*AQP2*) (1). Although more than 200 mutations of the *AVPR2* gene have been described that cause complete ADH resistance (2), only a few have caused partial ADH resistance (3,4).

In this case report, we present a newborn who was admitted to the neonatal intensive care unit (NICU) with hypernatremic dehydration and was eventually diagnosed

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with NDI due to a novel missense mutation (c.632T>C, p.L211P) in the *AVPR2* gene. The aim of this report is to highlight and discuss potential pitfalls in the management of neonatal NDI.

Case Report

A nineteen-day-old male was transferred to our unit with a clinical suspicion of diabetes insipidus (DI). He was born to a 22-year-old mother in the 39th week of gestation with no complications. The birth weight, height, and head circumference were 4160 g, 52 cm, and 37 cm, respectively. The parents were third-degree cousins and a maternal aunt had died at one month of age because of an unknown cause (Figure 1A). The mother had no complaints during pregnancy; however, mild fetal hydronephrosis had been detected on antenatal ultrasound in her third trimester of gestation. The baby was discharged with no problem and a recommendation for breastfeeding. He had been taken to another medical center at the age of 11 days with fever and restlessness. The serum sodium concentration was measured as 155 mEq/L. The patient had been admitted to NICU for hypernatremic dehydration, which had been interpreted as related to neonatal sepsis. The serum sodium level had increased to 161 mEq/L under rehydration treatment with 1/3 isotonic saline. The urine output was as high as 10-12 mL/kg/hour with a simultaneous plasma ADH level of 16 pg/mL (normal range: 2-12 pg/mL for a serum osmolality of >290 mOsm/kg). His volume resuscitation treatment had been made by large volumes of intravenous fluids (240-260 mL/kg/day) to compensate for the increased urinary output (>10 mL/kg/hour) and insensible fluid loss. The concentration of the intravenous fluid had gradually been decreased to 1/8 of normal saline and then switched to 5% dextrose with no sodium. On the nineteenth postnatal day, the baby was referred to our NICU for further investigation.

On physical examination, he appeared well and active with no remarkable pathologic findings. The weight was 4290 g. His serum sodium level was 149 mEq/L while he was receiving a 5% dextrose solution as 100% replacement volume for urinary output. Serum urea, creatinine, potassium, calcium, phosphate, alkaline phosphatase and magnesium, and capillary blood gas levels were all in normal ranges. Renal ultrasound showed grade 2 pelvicaliectasis in the right and grade 1 in the left kidneys. Urine output was measured as 11 mL/kg/hr on the first day in our unit.

An intranasal desmopressin test using 10 µg desmopressin acetate (DDAVP, Minirin® nasal spray, Ferring GmbH, Kiel, Germany) (a synthetic arginine vasopressin analogue) was performed to make the differential diagnosis of DI. Since the urine density increased from 1005 to 1022 six hours after the first administration of desmopressin and urine output decreased to 9.9 mL/kg/hr, suggesting central DI (CDI), treatment with 7.5 µg/day DDAVP (Minirin® Melt tablet) was started. However, urine output continued to be as high as 10-12 mL/kg/hour with a density of <1003 in the follow-up, despite gradually increasing doses of DDAVP up to 120 µg/day in the following four days. Based on this clinical observation, DDAVP was discontinued and hydrochlorothiazide was started at a dose of 1 mg/kg/day, a hypo-osmolar formula was given, and genetic analysis was planned for NDI. After rearrangement of treatment the urine volume decreased from 9.2 mL/kg/hour to 6.7 mL/kg/hour, and serum sodium levels were stabilized between 135-145 mEq/L (Figure 1B).

Meanwhile, it was learned that the mother also had polyuria and polydipsia. She used to drink about 15 to 20 litres of water per day, but she had never attended a doctor for this symptom. The genetic analyses revealed that both the mother and the infant had heterozygous and hemizygous missense mutations (c.632T>C, p.L211P), which had not been previously reported in large population databases, including ExAC, 1000 Genomes, 6500ESP and gnomAD. The pathogenicity of the variant was predicted using *in silico* tools (Polyphen-2, Sort Intolerant from Tolerant 'SIFT', and MutationTaster). Leucine (Leu; L) at position 211 in the AVPR2 protein which is located in the fifth helix in the cytoplasmic domain (Figure 2A, 2B). This change of Leu211 to Pro211 is predicted to be pathogenic and impair the interaction of AVPR2 and ADH by changing the three-dimensional structure of AVPR2 protein (Figure 2C).

Discussion

The diagnostic process and management of a newborn with NDI caused by a novel missense mutation (c.632T>C, p.L211P) in the *AVPR2* gene is described. The initial diagnosis was CDI, due to a positive response to DDAVP. However, the failure of ADH treatment during the clinical follow-up led to consideration of a diagnosis of NDI, which has been termed "AVP resistance" (5). The patient was successfully treated with hydrochlorothiazide and hypo-osmolar formula.

Hypernatremic dehydration is common in the neonatal period. Three pathophysiologic mechanisms may underlie the etiology: 1) decreased water intake; 2) increased water loss; or 3) increased intake of sodium. Treatment depends on the severity of dehydration and hypernatremia and consists of fluid therapy to replace fluid loss, maintenance fluids, and insensible loss. Due to the risk of brain edema, it

is strongly recommended that serum sodium should not be decreased more than 10 meq/L in 24 hours (1).

Hypernatremia in DI develops due to impaired water reabsorption and increased water loss. The symptoms are non-specific and may be confused with other disorders. Restlessness, vomiting, fever, lethargy, dehydration and polyuria are common (6,7). Unlike adults, neonates are unable to access water themselves when thirsty, which makes them prone to hypernatremia. Despite dehydration, frequent and heavy nappies suggesting polyuria are important clues for DI, but are usually overlooked by both the family and health workers (8,9). Once the diagnosis is established, treatment is the same as the other aetiologies

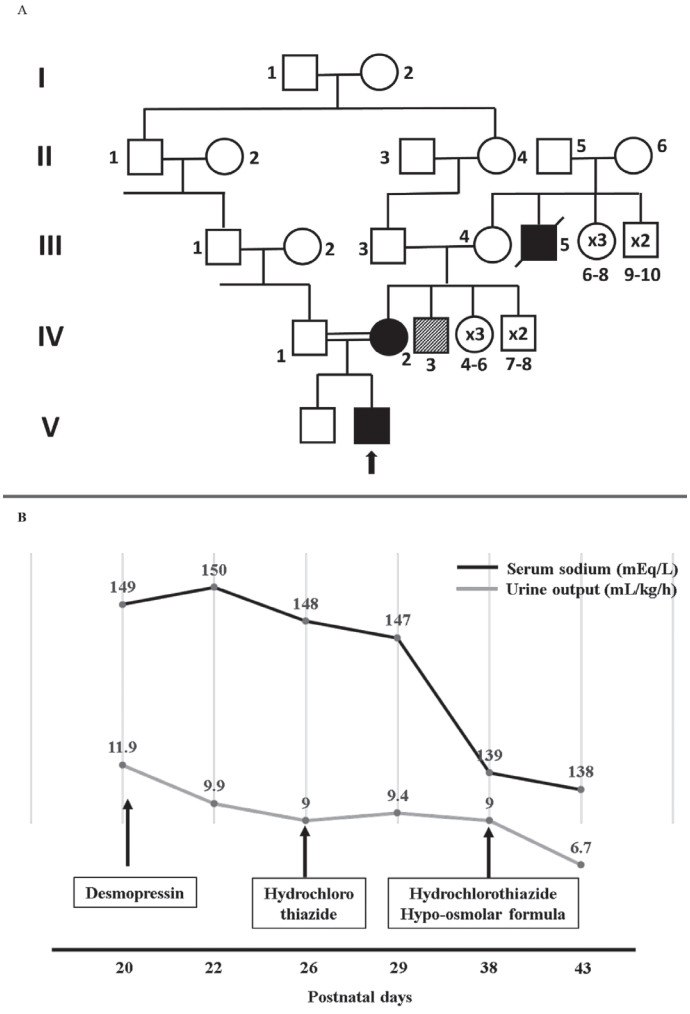

Figure 1. Clinical characteristics of the patient with nephrogenic diabetes insipitus due to mutation in *AVPR2* gene. A) Pedigree of the patient and his family. Individual IV.2 is heterozygous for *AVPR2* c.632T > C. Individual V.2 is hemizygous for AVPR2 c.632T > C. Genetic analysis could not be performed in II.6, III.4, III.5, and IV.3. Slash-line square (IV.3) indicates maternal uncle with polyuria, polydipsia and mental retardation. B) The urine output and serum sodium concentrations of the patient with nephrogenic diabetes insipidus during the clinical follow-up

of hypernatremic dehydration except the concentration of fluid should be more hypotonic than for neonates with deficient intake. Another important aspect is that the total volume of fluid replacement cannot be easily decreased in these patients because of extremely high urine output which sometimes reaches to 10 mL/kg/hour and continues indefinitely unless treated with effective drugs. After stabilizing serum sodium and water homeostasis, discharge of these babies warrants family education about the disease, emergency situations and compliance to therapy.

ADH functions to control reabsorbtion of water in both volume depletion or increased serum osmolality. Therefore, impaired ADH production or resistance to its effect causes central or nephrogenic DI, respectively. A water deprivation test is not suggested in neonates and very young infants (8). Thus, a desmopressin test may be used to decide whether DI is central (ADH-responsive), or nephrogenic (ADH-not responsive) with close follow up of urinary density and amount of urinary output. Partially responsive NDI cases have been reported and treatment with DDAVP may be successful (3,4,7,10,11,12).

Ninety percent of congenital NDI is caused by a mutation in *AVPR2*, located on the X chromosome (1). Therefore, mainly males are affected. Female carriers may have NDI depending on the extent of genomic inactivation of the healthy X chromosome, which we suggest may have occurred in the mother of our patient (13). We could not perform studies showing X chromosome inactivation in the mother. The other 10% of NDI cases are due to aquaporin gene mutation, which is inherited in both autosomal recessive or dominant patterns (1). Congenital CDI is rarely seen and usually present after one year of age (6). History of polyhydramnios or fetal hydronephrosis, and family history of an X-linked pattern of inheritance, as in the presented case, should suggest NDI.

We have identified a novel missense mutation in *AVPR2*, in both the patient and his mother as the cause of NDI. To date, over 200 mutations in the *AVPR2* gene have been described, but only a few of the reported mutations cause partial NDI (3). The AVPR2 protein has 371 amino acids, three extracellular and three intracellular loops with seven transmembrane domains (2). The severity of NDI depends on the type of mutation (2,14,15,16,17). Some mutations lead to partial response to ADH, whereas the others cause complete ADH resistance. In some mutations the AVP protein is produced but trapped in the endoplasmic reticulum without being transferred to the cell membrane (14). In the presented case, the change of Leu211 to Pro211 is predicted to impair the interaction of AVPR2 and ADH by changing

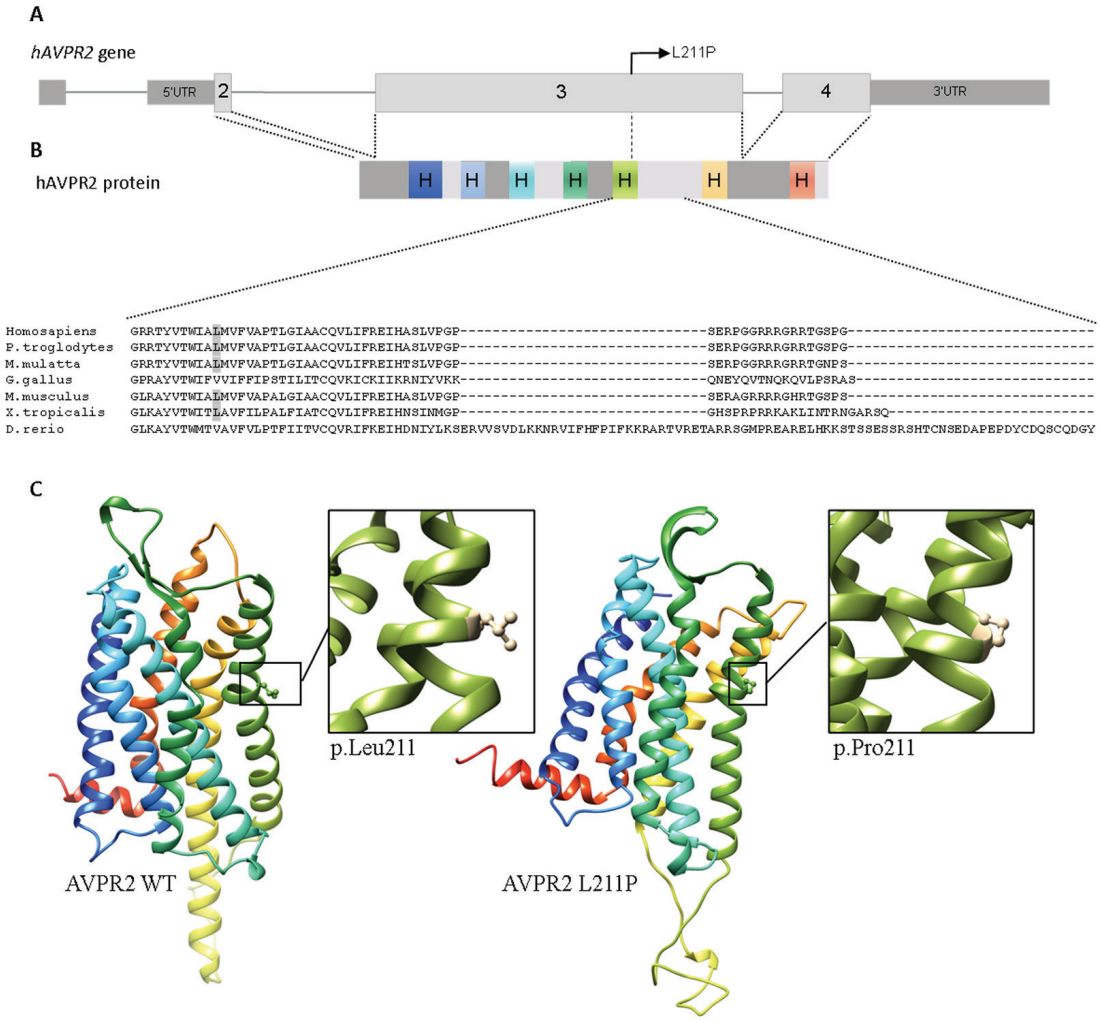

Figure 2. Molecular characteristics of wild type and mutant *AVPR2* gene and AVPR2 protein. A) Diagram of h*AVPR2* gene (NM_000054.6): Arrow shows novel missense variant (L211P) identified in the patient and his mother. B) Structure of AVPR2: Dark grey and light grey indicates extracellular and cytoplasmic components of AVPR2, respectively. H: Transmembrane helical components of AVPR2; painted with corresponding colors of the helixes in three-dimensional structure of protein. Partial alignment of AVPR2 protein sequences, generated by Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/), showing conservation of leucine (Leu; L) at position 211, highlighted in grey. C) Three-dimensional protein structures for wild-type and mutant proteins were obtained with Swiss-Model and UCSF Chimera 1.10.2 servers, and rainbow-painted from dark blue for N-terminal to red for C-terminal. The Leu211 and Pro211 residues are presented in a magnified frame for viewing at a higher quality and indicated in yellow

the three-dimensional structure of the AVPR2 protein. This may have caused an initial response to DDAVP but later the patient became unresponsive, which can be explained by residual mutant ADH receptor activity responsible for the partial ADH response. Severe ADH resistance may also cause over-expression of AVPR2 on the membrane surface of the principal cells of the renal collecting ducts, which may also lead to a partial ADH response.

The medical therapy for NDI includes the use of diuretics and non-steroidal anti-inflammatory drugs (NSAIDs). In volume depletion states, thiazide diuretics reduce urine output by blocking the sodium-chloride co-transporter in the distal convoluted tubule and thus increase the reabsorption of sodium and water in the proximal tubule (1,10). Hydrochlorothiazide at 2 to 4 mg/kg/day in twice-daily doses is the initial treatment for NDI. It can decrease urine output by as much as 50% (1). The loss of potassium, which is induced by thiazide diuretics, may require adding of potassium-sparing diuretics, such as amiloride, to the treatment. NSAIDs, such as ibuprofen and indomethacin, can be used in combination with diuretics in NDI. Prostaglandin inhibitors reduce urinary output with a mechanism independent of vasopressin,

and renal function must be closely monitored in patients using prostaglandin inhibitors (18). In patients who cannot tolerate indomethacin because of gastric side effects, selective inhibitors of cyclooxygenase-2 might be helpful.

More recently, AVPR2 receptor antagonists and agonists, vasopressin analogues, prostaglandin receptor agonists, secretin receptor agonists and cGMP phosphodiesterase inhibitors have been found beneficial in model organisms, which activate secondary intracellular messengers through alternative pathways (1,19).

In infants, early recognition of NDI and treatment is very important as the proper treatment can avert the physical and mental retardation that results from repeated episodes of dehydration and hypernatremia. The presented patient is still under follow-up at pediatric endocrinology and nephrology. At the last examination, he was 4 years and 10 months old. His weight and height were 17.5 kg [0.04 standard deviation score (SDS)] and 103 cm (-0.73 SDS), respectively. Neuromotor development was normal.

Conclusion

In conclusion, hypernatremic dehydration with hypotonic polyuria in a newborn should evoke the suspicion of DI. Characteristics suggesting antenatal onset and X-linked inheritance are important clinical clues for the diagnosis of congenital NDI. However initial or partial DDAVP response may complicate the diagnostic process of NDI, as in our case who was found to harbor a novel missense (c.632T>C, p.L211P) *AVPR2* mutation. Early recognition and appropriate management of NDI may prevent potentially life-threatening hypernatremic dehydration in young infants.

Ethics

Informed Consent: The patient's parents provided informed consent for publication of this case report.

Footnotes

Authorship Contributions

Concept: Ömer Güran, Design: Ömer Güran, Data Collection or Processing: Ömer Güran, Serçin Güven, Heves Kırmızıbekmez, Özlem Akgün Doğan, Leyla Karadeniz Bilgin, Literature Search: Ömer Güran, Serçin Güven, Heves Kırmızıbekmez, Özlem Akgün Doğan, Leyla Karadeniz Bilgin, Writing: Ömer Güran, Leyla Karadeniz Bilgin.

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